

## REMARKS

The present invention relates to a method of treating a patient suffering from a brain or spinal cord injury or neurodegenerative disease using cells derived from bone marrow. Claims 1-4 are currently pending and under consideration in the present application.

Claim 4 has been amended herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. No new matter has been added by way of this amendment as more fully discussed below.

### Supplemental Information Disclosure Statement

The Examiner has indicated that the Information Disclosure Statement ("IDS") filed on June 4, 2003 does not comply with current PTO practice. Specifically, the Examiner contends that the IDS should identify each cited reference by name and date.

As an initial matter, Applicants respectfully point out that the Examiner has initialized all the references cited on the Form PTO-1449 with the exception of the listed U.S. Patent documents. It is Applicants' understanding that the Examiner did not consider the listed U.S. Patent documents because the references were not identified by name and date. In any event, the Examiner has also cited in Form PTO-892 (Notice of Referenced Cited), which accompanied the present Office Action, the identical U.S. Patent Documents listed on the Form PTO-1449 that are at issue at this time.

In view of the fact that the Examiner has cited the identical references that were not considered on Form PTO-1449 submitted by Applicants, the filing of a Supplemental IDS is not necessary at this time since these references have been made of record by the Examiner.

### Amendment to the Specification to add the abstract

The Examiner has indicated that the specification does not comply with current PTO practice with respect to the abstract as required under 37 CFR §1.72(b). 37 CFR §1.72(b) states that the abstract must commence on a separate sheet. Applicants respectfully point out that the abstract was filed as part of the application as being on the front page of International Patent Application No. PCT/US00/12875. Applicants further submit that by way of Preliminary Amendment dated November 2, 2001, which was filed concomitantly with the Transmittal Letter concerning a filing under 35 U.S.C. §371 and the present application, the specification of the

present application was amended to recite that the present application claims the benefit of priority to PCT/US00/12875, filed May 11, 2000. As such, Applicants contend that the present application was properly filed under 35 § U.S.C. 371 and that the abstract was properly filed as part of the present application.

In any event, Applicants herein have amended the specification to have the abstract be added to the specification on a separate sheet, and in particular, to have the abstract commence on a separate sheet following the “CLAIMS” section. The Abstract added herein is identical to the Abstract on the front page of PCT/US00/12875. As such, no new matter has been added by way of the present amendment.

#### Amendment to claim 4

Applicants have amended claim 4 herein to more particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Specifically, claim 4 has been amended to recite a method of treating injured brain or spinal cord in a patient by injecting or transplanting a composite of mesenchymal stem cells (MSCs) and neurospheres into said patient. Support for the amendment to claim 4, is found throughout the as-filed specification. For example, beginning on line 17 of page 19, the as-filed specification teaches transplantation of MSC and neurosphere into a mammal suffering from stroke or traumatic brain injury to treat such conditions. As such, Applicants respectfully submit that amended claim 4 is supported by the as-filed specification and therefore the amendment to claim 4 does not constitute new matter.

#### Rejection of claims 1-4 pursuant to 35 U.S.C. §102(b)

The Examiner has rejected claims 1-4 under 35 U.S.C. §102(b). Specifically, the Examiner asserts that Azizi et al. (1998, PNAS 95:3908-3913) teaches transplantation of human marrow stromal cells and astrocyte precursors (which the Examiner considers to be neurospheres) into a mammal. In addition, although the Examiner concedes that Azizi transplants these cells into healthy brains, the Examiner contends that the transplantation of such cells would treat a diseased or injured central nervous system. Therefore, the Examiner is of the opinion that Azizi meets the limitations of the claimed invention. Applicants respectfully submit that Azizi does not anticipate the present invention for the following reasons.

It is hornbook law that “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). “The identical invention must be shown in as complete detail as is contained in the . . . claim.” *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added)). Therefore, Azizi must describe each and every element of claims 1-4 in order to anticipate these claims under 35 U.S.C. §102(b), and this reference does not satisfy this requirement.

The present invention encompasses treating a patient suffering from a brain or spinal cord injury or neurodegenerative disease using cells derived from bone marrow. Applicants respectfully assert that Azizi does not anticipate the present invention because Azizi merely teaches engraftment and migration of bone marrow stromal cells following transplantation into the brain. Nowhere does Azizi teach that administering such cells into the brain of a recipient would result in a therapeutic effect. The experiments performed by Azizi were to demonstrate that human bone marrow stromal cells that were infused into a rat brain could engraft, migrate, and survive in a manner similar to rat astrocytes (see first paragraph on page 3912) that were infused into an otherwise identical rat brain. At best, the results from Azizi demonstrate survival of bone marrow stromal cells and astrocytes following injection into the corpus striatum of rat brains and that each cell type migrated from the site of injection into multiple areas of the brain including the contralateral cortex. However, nowhere does Azizi teach that these cells are transplanted into a patient that is suffering from a brain or spinal cord injury or neurodegenerative disease. Rather, Azizi teaches the administration of the cells into brains of normal, healthy rats. Furthermore, nowhere does Azizi teach that administering such cells would result in a therapeutic effect whereby the patient would be treated from a brain or spinal cord injury or neurodegenerative disease. Azizi does not teach any behavioral tests performed on any animals following receipt of the transplantation of the cells, and therefore Azizi does not offer any indication that the transplanted cells would result in a therapeutic effect.

With respect to the Examiner’s assertion that although Azizi teaches transplantation of bone marrow stromal cells into healthy brains of rats, the teachings of Azizi would still anticipate the present invention because Azizi suggests the use of the cells to treat a variety of diseases of the central nervous system, Applicants disagree with the Examiner’s

reasoning and respectfully submit that Azizi does not anticipate the present invention for the following reasons.

Applicants assert that a mere statement that the cells may be used for both cell and gene therapy for a variety of diseases of the central nervous system is not enabling and therefore can not be a prior art reference under 35 U.S.C. § 102(b). It is hornbook law that for the purposes of 102(b), "...even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling". *In re Donohue*, 766 F.2d 531 at 533, USPQ 619 (Fed. Cir. 1985). Azizi does not provide an enabling disclosure of a method of treating a patient suffering from a brain or spinal cord injury or neurodegenerative disease using cells derived from bone marrow.

In order to anticipate the present invention, a reference must provide an enabling disclosure of the invention, which Azizi fails to do. Moreover, in order to be enabling, a prior art reference must teach one of ordinary skill in the art how to make the claimed invention with no undue experimentation. *Minnesota Mining and Manufacturing Co. v. Chemque, Inc.*, 303 F.3d 1294, 1301 (Fed. Cir. 2002). *In re Wands* (858 F.2d 731 (Fed. Cir. 1988) provides the factual premises considered when determining whether the amount of experimentation is undue.

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *In re Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands* (858 F.2d 731, 737 (Fed. Cir. 1988) (citations omitted).

Not every Wands factor must be considered to find Azizi non-enabling. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991). Therefore, in order to anticipate claims 1-4, Azizi must not only enable a method of treating a patient suffering from a brain or spinal cord injury or neurodegenerative disease using cells derived from bone marrow, Azizi must do so without requiring undue experimentation, as determined by the *Wands* factors. Azizi fails to accomplish this.

As discussed above, Azizi at best teaches survival, engraftment, and migration of marrow stromal cells following transplantation into brains of normal, healthy rats, and broadly

speculates that the cells can be used to treat diseases of the central nervous system (Abstract). Not only does Azizi teach administering the cells into brains of normal, healthy rats, but nowhere does Azizi administer the cells into brains of rats that have been subjected to conditions that would amount to a diseased state. Upon reading Azizi, the skilled artisan is given no reason to believe that administering the cells to a patient in need thereof would be a successful treatment of a disease. Therefore, one of skill in the art would be required, when armed with the teachings of Azizi, to perform further experimentation. In accordance with the *Wands* factors, Azizi requires undue experimentation in order to practice the present invention as recited in the pending claims. Moreover, given that the biotechnology arts are viewed as unpredictable by the United States Patent and Trademark Office, Azizi's blanket statement that these cells can be used to treat various diseases of the central nervous system cannot be deemed as a statement with a predictable result, unless Azizi provides some evidence to support this assertion. Therefore, according to the *Wands* factors, Azizi does not enable treatment of a brain or spinal cord injury or neurodegenerative disease using cells derived from bone marrow.

The *Wands* factors also consider the presence or absence of working examples, which are decidedly missing from Azizi. In fact Azizi presents no working examples of the treatment of various diseases of the central nervous system in any animal model suffering from such diseases. That is, Azizi only administers the cells into brains of normal, healthy rats. The present application, conversely, presents working examples for administering the cells into animals suffering from a brain or spinal cord injury or neurodegenerative disease for the treatment thereof. Further, without working examples, or even prophetic examples for that matter, the Azizi reference does not provide enough guidance to enable its own disclosure. The skilled artisan is provided with no more than a mere suggestion based on pure speculation that diseases of the central nervous system can be treated using bone marrow stromal cells. While the skill in the medical biotechnology arts may be quite competent, it is not so elevated that the skilled artisan, equipped with the instruction to administer bone marrow stromal cells into a healthy rat brain, could glean a successful treatment of a patient suffering from a brain or spinal cord injury or neurodegenerative diseases from the teachings of Azizi. Therefore, the overreaching statement that various diseases of the central nervous system can be treated using bone marrow stromal cells is not enabled in view of the standards set forth under of 35 U.S.C. §102(b).

Applicants respectfully submit that claims 1-4 are not anticipated by Azizi et al. for the reasons set forth above, and request reconsideration and withdrawal of the rejection pursuant to 35 U.S.C. §102(b).

Rejection of claims 1-4 pursuant to 35 U.S.C. §102(b) in view of Kohyama

The Examiner has rejected claims 1-4 under 35 U.S.C. §102(b), because the Examiner contends that Kohyama et al. (2001 Differentiation 68:235-44) renders claims 1-4 anticipated. Applicants point out that the present application is a U.S. national phase application filed under 35 U.S.C. § 371 claiming benefit to International Application PCT/US00/12875, filed May 11, 2000, which claims the benefit of priority to U.S. Provisional Patent Application No. 60/134,344, filed May 14, 1999.

Applicants respectfully submit that the priority was correctly claimed on the Transmittal Letter to The United States Designated/Elected Office (EO/EO/US) Concerning a Filing Under 35 § U.S.C. 371 filed on November 2, 2001, in order to enter in the national stage in the United States. Further, Applicants respectfully point out to the Examiner that the Filing Receipt indicates that the U.S.P.T.O. recognized that the present application is a U.S. national phase application filed under 35 U.S.C. § 371 of International Application No. PCT/US00/12875, filed May 11, 2000, which claims benefit to U.S. Provisional Patent Application 60/134,344, filed May 14, 1999. Thus, Kohyama can not be a prior art reference under 35 U.S.C. § 102(b) to anticipate the pending claims because the priority date of the present application predates the publication date of Kohyama et al. of October 2001.

Applicants respectfully submit that for the reasons set forth above, the rejection of claims 1-4 pursuant to 35 U.S.C. §102(b) in view of Kohyama et al. is rendered moot.

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-4 are now in condition for allowance

Respectfully submitted,

**YI LI ET AL.**

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(Date)

By:

Kathryn Doyle  
**KATHRYN DOYLE, Ph.D, J.D.**  
Registration No. 36,317  
**MORGAN, LEWIS & BOCKIUS, LLP**  
1701 Market Street  
Philadelphia, PA 19103-2921  
Telephone: (215) 963-5000  
**Direct Dial: (215) 963-4723**  
Facsimile: (215) 963-5001  
E-Mail: [kdoyle@morganlewis.com](mailto:kdoyle@morganlewis.com)  
Attorney for Applicants

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